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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,172	11/16/2001	Avi J. Ashkenazi	P2730P1C50	3269

35489 7590 03/24/2004

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,172	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-128 and 130-138* is/are rejected.

7)☒ Claim(s) *129* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence comparison*.

DETAILED ACTION

The preliminary amendment filed 11/16/01 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 132, 133 and dependent claims 134-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 132 and 133 are indefinite because the metes and bounds of the claims are not clear. For claim 132 it is not clear if hybridization under any condition is permissible, even the most permissive, allowing non-specific hybridization to occur. For claim 133, while the skilled artisan understands the general concept of hybridization under "stringent conditions", what specific conditions are intended by the use of the term "stringent" in the present claims is unknown. What conditions of stringency are used in any particular situation are determined by the specificity of hybridization desired by the practitioner. The instant specification presents examples but not a limiting definition of "stringent conditions" (p. 312, line 23, through p. 313, line 4). In this case, the desired specificity is unknown. "Stringent" carries a meaning of "constricted", implying that not all hybridization conditions are acceptable. If however, there is a structural relatedness (limitation) that is being defined by the conditions, then those conditions or range of conditions must be clear in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-124, 127, 128 and 132-134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID

NO:51 or which encodes the protein of SEQ ID NO:52 or the protein of SEQ ID NO:52 except lacking its associated signal sequence, does not reasonably provide enablement for other nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nucleic acid of SEQ ID NO:52 encodes a protein called PRO1282 which is 673 amino acids long, with a putative signal sequence from residue 1-23, transmembrane domain from 579-599, leucine zipper region from 197-269 and EGF-like domain beginning at 430 (p. 414, lines 13-16). The encoded protein tested positive in the Chondrocyte Redifferentiation Assay (#110, p. 530) and the nucleic acid was shown to have a ΔCt slightly greater than 1 for 2/17 colon tumors (ΔCt =1.15 and 1.07) tested and none of the 12 lung tumors tested (p. 554).

The claims are broad, including nucleic acids encoding only an extracellular domain of SEQ ID NO:52 and nucleic acids 80% identical to thereto. There is no functional limitation associated with the nucleic acid or encoded protein in the claims. Aside from the positive outcome in the chondrocyte redifferentiation assay there is no function associated with PRO1282, and its specific role in the redifferentation is not disclosed.

Blast results submitted by Applicant and other sequence comparison shows that PRO1282 is most structurally related to slit and riken proteins, however, the function of these proteins is unclear. Itoh et al. cloned human homologues of Drosophila slit and suggests a possible role for mammalian slit in formation and maintainence of the nervous and endocrine system based on its role in Drosophila and its tissue expression in human

and rat (p. 185, 2 paragraphs beginning the last paragraph of col. 1). It is also noted that Drosophila slit is not expressed in neuronal cells, but rat slit-1 and human slit-1, -2 and -3 are (last 2 sentences of last paragraph in col. 1, p. 185). The prior art does not provide sufficient information to allow the skilled artisan to use PRO1282 or the encoding nucleic acid without significant further research.

While the nucleic acid showed slight amplification in 2 tumor cells lines compared to normal tissue, this does not support a diagnostic use of the nucleic acid for detection of cancerous tissue. There are several reasons for this. Elevated copy number in 2/17 colon cancers does not provide the skilled artisan with a reasonable expectation that PRO1218 DNA copy number can serve as a marker for colon cancer since expression was in such a small minority of the tumors tested. Further, Lanza et al. (Cancer, 82:49, 1998) showed that out of 191 colon carcinomas tested, 144 (75.4%) had aneuploid DNA (p. 51, col. 2, third full paragraph). That means an increased copy number for PRO1218 in the colon tumors tested was less like due to an increase unique to PRO1282 DNA, but rather due to a more general phenomenon of aneuploidy of the DNA in those colon cancer cells. Another study of aneuploidy in colon cancers showed that in some individuals with colon cancer, aneuploidy was also found in morphologically normal colon tissue (Fleischhacker et al., Modern Path., 8:360, 1995; *e.g.,* p. 360, col. 2). Because aneuploid DNA can be found in normal tissue, detection of increased DNA copy number does not necessary mean those cells containing the DNA are cancerous. Further, the ΔCt's of the PRO1282 DNA were extremely low, and the specification says on p. 548, lines 35-36, that "...the CT value of normal human DNA subtracted from test DNA was +/-1 Ct." In light of this, it is questionable whether a CT value of 1.07 or even 1.15 can be considered significant. Therefore in this instance, copy number does not support a basis for how to use the claimed nucleic acid.

While the PRO1282 protein (probably the mature form) lead to redifferentation in the chondrocyte assay, the specification provides no information on what domains or characteristics of the protein were responsible for its effect on chondrocytes. It is unpredictable if the extracellular domain alone has the necessary function. Indeed, one skilled in the art would expect that signal transduction would be necessary for

chondrocyte redifferentiation, and a soluble polypeptide cannot transduce a signal unless it is a soluble ligand able to bind to and activate a receptor. The structural elements identified by Applicants for PRO1282 makes it unlikely that it is normally a soluble ligand. Based on PRO1282's homology to slit discussed above, one could not have predicted a reasonable expectation of successful in cause chondrocyte redifferentation. While the PRO1282 protein of SEQ ID NO:52 (with or without the signal sequence) was functional in this assay, it is, at the least, unpredictable what changes could be made to SEQ ID NO:52 while retaining its redifferentation ability.

For these reasons which include breadth of the claims, lack of information on the relationship of structure to function of PRO1282, paucity of information in the prior art, limited working example, and lack of guidance for use provided in the specification, it would require undue experimentation to use the claimed nucleic acid commensurate in scope with the claims.

Claims 119-124, 127, 128 and 132-134 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid having at least 80%, 85%, 90%, 95% or 99% sequence identity to a nucleic acid encoding a polypeptide with a particular disclosed sequence or drawn to a nucleic acid that hybridizes to SEQ ID NO:51. The claims do not require that the nucleic acid or encoded polypeptide possess any particular biological activity, nor any particular conserved structure or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any

combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Which nucleic acids of the genus comprising the required sequence are part of the invention has not been set forth.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids comprising SEQ ID NO:51 or which encode the polypeptide of SEQ ID NO:52, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Priority

Priority application 09/380,137 and earlier filed priority applications do *not* meet the requirements of 35 U.S.C. § 112, first paragraph. Because there was no function associated with PRO1282 and the skilled artisan would not have known how to use it, the prior application also does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120. Note that even if priority were granted to the earliest filed priority application 60/097,979, the art rejection below would remain under 35 UCS 102(e).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-128 and 130-138 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,225,085.

US 6,225,085 teaches a LRSG (leucine-rich surface glycoprotein) of SEQ ID NO:2 which is identical to SEQ ID NO:52 of the instant application. The coding region of the LRSG nucleic acid is identical to that of SEQ ID NO:51 (see attached SEQUENCE COMPARISON). Also disclosed is the encoded protein without or optionally with its signal sequence or with only an extracellular domain (col. 7, lines 1-27), as well as the nucleic acid in a vector and expressed in, for example, *E. coli* (*e.g.*, col. 28, lines 28-45).

Claim Objections

Claim 129 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

March 17, 2004

SEQUENCE COMPARISON OF SEQ ID NO:52 WITH US 6,225,085

; Sequence 2, Application US/09063950C
; Patent No. 6225085
; GENERAL INFORMATION:
; APPLICANT: Holtzman, Douglas A.
; TITLE OF INVENTION: NOVEL LRSG PROTEIN AND NUCLEIC ACID MOLECULES AND USES
; TITLE OF INVENTION: THEREFOR
; CURRENT APPLICATION NUMBER: US/09/063,950C
; CURRENT FILING DATE: 1998-04-21
; SEQ ID NO 2
; LENGTH: 673
; TYPE: PRT
; ORGANISM: Homo sapiens
US-09-063-950-2

Query Match 100.0%; Score 3520; DB 3; Length 673;
Best Local Similarity 100.0%; Pred. No. 5.8e-249;
Matches 673; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 MCSRVPLLLPLLLLLALGPGVQGCPSGCQCSQPQTVFCTARQGTTVPRDVPPDTVGLYVF 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MCSRVPLLLPLLLLLALGPGVQGCPSGCQCSQPQTVFCTARQGTTVPRDVPPDTVGLYVF 60

Qy         61 ENGITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETF 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 ENGITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETF 120

Qy        121 RGLRRLERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNS 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 RGLRRLERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNS 180

Qy        181 LLALEPGILDTANVEALRLAGLGLQQLDEGLFSRLRNLHDLDVSDNQLERVPPVIRGLRG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 LLALEPGILDTANVEALRLAGLGLQQLDEGLFSRLRNLHDLDVSDNQLERVPPVIRGLRG 240

Qy        241 LTRLRLAGNTRIAQLRPEDLAGLAALQELDVSNLSLQALPGDLSGLFPRLRLLAAARNPF 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 LTRLRLAGNTRIAQLRPEDLAGLAALQELDVSNLSLQALPGDLSGLFPRLRLLAAARNPF 300

Qy        301 NCVCPLSWFGPWVRESHVTLASPEETRCHFPPKNAGRLLLELDYADFGCPATTTTATVPT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 NCVCPLSWFGPWVRESHVTLASPEETRCHFPPKNAGRLLLELDYADFGCPATTTTATVPT 360

Qy        361 TRPVVREPTALSSSLAPTWLSPTAPATEAPSPPSTAPPTVGPVPQPQDCPPSTCLNGGTC 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 TRPVVREPTALSSSLAPTWLSPTAPATEAPSPPSTAPPTVGPVPQPQDCPPSTCLNGGTC 420

Qy        421 HLGTRHHLACLCPEGFTGLYCESQMGQGTRPSPTPVTPRPPRSLTLGIEPVSPTSLRVGL 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 HLGTRHHLACLCPEGFTGLYCESQMGQGTRPSPTPVTPRPPRSLTLGIEPVSPTSLRVGL 480

Qy        481 QRYLQGSSVQLRSLRLTYRNLSGPDKRLVTLRLPASLAEYTVTQLRPNATYSVCVMPLGP 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 QRYLQGSSVQLRSLRLTYRNLSGPDKRLVTLRLPASLAEYTVTQLRPNATYSVCVMPLGP 540
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Qy        541 GRVPEGEEACGEAHTPPAVHSNHAPVTQAREGNLPLLIAPALAAVLLAALAAVGAAYCVR 600
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Db        541 GRVPEGEEACGEAHTPPAVHSNHAPVTQAREGNLPLLIAPALAAVLLAALAAVGAAYCVR 600

Qy        601 RGRAMAAAAQDKGQVGPGAGPLELEGVKVPLEPGPKATEGGGEALPSGSECEVPLMGFPG 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 RGRAMAAAAQDKGQVGPGAGPLELEGVKVPLEPGPKATEGGGEALPSGSECEVPLMGFPG 660

Qy        661 PGLQSPLHAKPYI 673
              |||||||||||||
Db        661 PGLQSPLHAKPYI 673
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SEQUENCE COMPARISON OF SEQ ID NO:51 WITH US 6,225,085

; Sequence 1, Application US/09063950C
; Patent No. 6225085
; GENERAL INFORMATION:
; APPLICANT: Holtzman, Douglas A.
; TITLE OF INVENTION: NOVEL LRSG PROTEIN AND NUCLEIC ACID MOLECULES AND USES
; TITLE OF INVENTION: THEREFOR
; FILE REFERENCE: MEI-019
; CURRENT APPLICATION NUMBER: US/09/063,950C
; CURRENT FILING DATE: 1998-04-21
; NUMBER OF SEQ ID NOS: 9
; SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 1
; LENGTH: 2852
; TYPE: DNA
; ORGANISM: Homo sapiens
; FEATURE:
; NAME/KEY: CDS
; LOCATION: (160)..(2178)
US-09-063-950-1

Query Match 99.5%; Score 2754.4; DB 3; Length 2852;
Best Local Similarity 99.9%; Pred. No. 0;
Matches 2767; Conservative 0; Mismatches 1; Indels 2; Gaps 1;

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Qy=NO:51     1 ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCTCGGGCCCGACCCGCCAGGAAAGAC 60
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          41 ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCTCGGGCCCGACCCGCCAGGAAAGAC 100

Qy          61 TGAGGCCGCGGCCTGCCCCGCCCGGCTCCCTGCGCCGCCGCCGCCTCCCGGGACAGAAGA 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         101 TGAGGCCGCGGCCTGCCCCGCCCGGCTCCCTGCGCCGCCGCCGCCTCCCGGGACAGAAGA 160

Qy         121 TGTGCTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGG 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         161 TGTGCTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGG 220

Qy         181 TGCAGGGCTGCCCATCCGGCTGCCAGTGCAGCCAGCCACAGACAGTCTTCTGCACTGCCC 240
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         221 TGCAGGGCTGCCCATCCGGCTGCCAGTGCAGCCAGCCACAGACAGTCTTCTGCACTGCCC 280

Qy         241 GCCAGGGGACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTG 300
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         281 GCCAGGGGACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTG 340

Qy         301 AGAACGGCATCACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCC 360
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         341 AGAACGGCATCACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCC 400

Qy         361 TGGACCTGTCACAGAACCAGATCGCCAGCCTGCCCAGCGGGGTCTTCCAGCCACTCGCCA 420
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         401 TGGACCTGTCACAGAACCAGATCGCCAGCCTGCCCAGCGGGGTCTTCCAGCCACTCGCCA 460

Qy         421 ACCTCAGCAACCTGGACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCC 480
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         461 ACCTCAGCAACCTGGACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCC 520
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Qy        481 GTGGCCTGCGGCGCCTCGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGC 540
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Db        521 GTGGCCTGCGGCGCCTCGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGC 580

Qy        541 CTGGTGCCTTCGACACGCTCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGC 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        581 CTGGTGCCTTCGACACGCTCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGC 640

Qy        601 GGGCACTGCCCCCGCTGCGCCTGCCCCGCCTGCTGCTGCTGGACCTCAGCCACAACAGCC 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        641 GGGCACTGCCCCCGCTGCGCCTGCCCCGCCTGCTGCTGCTGGACCTCAGCCACAACAGCC 700

Qy        661 TCCTGGCCCTGGAGCCCGGCATCCTGGACACTGCCAACGTGGAGGCGCTGCGGCTGGCTG 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        701 TCCTGGCCCTGGAGCCCGGCATCCTGGACACTGCCAACGTGGAGGCGCTGCGGCTGGCTG 760

Qy        721 GTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACC 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        761 GTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACC 820

Qy        781 TGGATGTGTCCGACAACCAGCTGGAGCGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        821 TGGATGTGTCCGACAACCAGCTGGAGCGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCC 880

Qy        841 TGACGCGCCTGCGGCTGGCCGGCAACACCCGCATTGCCCAGCTGCGGCCCGAGGACCTGG 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        881 TGACGCGCCTGCGGCTGGCCGGCAACACCCGCATTGCCCAGCTGCGGCCCGAGGACCTGG 940

Qy        901 CCGGCCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCCTGCAGGCCCTGCCTG 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        941 CCGGCCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCCTGCAGGCCCTGCCTG 1000

Qy        961 GCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCCCGCAACCCCTTCA 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1001 GCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCCCGCAACCCCTTCA 1060

Qy       1021 ACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCTGGGTGCGCGAGAGCCACGTCACACTGG 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1061 ACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCTGGGTGCGCGAGAGCCACGTCACACTGG 1120

Qy       1081 CCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCAAGAACGCTGGCCGGCTGCTCCTGG 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1121 CCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCAAGAACGCTGGCCGGCTGCTCCTGG 1180

Qy       1141 AGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACCACAGCCACAGTGCCCACCA 1200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1181 AGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACCACAGCCACAGTGCCCACCA 1240

Qy       1201 CGAGGCCCGTGGTGCGGGAGCCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTA 1260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1241 CGAGGCCCGTGGTGCGGGAGCCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTA 1300

Qy       1261 GCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCACTGCCCCACCGACTGTAG 1320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1301 GCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCACTGCCCCACCGACTGTAG 1360
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Qy       1321 GGCCTGTCCCCCAGCCCCAGGACTGCCCACCGTCCACCTGCCTCAATGGGGGCACATGCC 1380
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1361 GGCCTGTCCCCCAGCCCCAGGACTGCCCACCGTCCACCTGCCTCAATGGGGGCACATGCC 1420

Qy       1381 ACCTGGGGACACGGCACCACCTGGCGTGCTTGTGCCCCGAAGGCTTCACGGGCCTGTACT 1440
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1421 ACCTGGGGACACGGCACCACCTGGCGTGCTTGTGCCCCGAAGGCTTCACGGGCCTGTACT 1480

Qy       1441 GTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCACGCCGAGGCCAC 1500
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1481 GTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCACGCCGAGGCCAC 1540

Qy       1501 CACGGTCCCTGACCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGC 1560
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1541 CACGGTCCCTGACCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGC 1600

Qy       1561 AGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACC 1620
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1601 AGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACC 1660

Qy       1621 TATCGGGCCCTGATAAGCGGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTGAGTACA 1680
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1661 TATCGGGCCCTGATAAGCGGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTGAGTACA 1720

Qy       1681 CGGTCACCCAGCTGCGGCCCAACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGGCCCG 1740
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1721 CGGTCACCCAGCTGCGGCCCAACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGGCCCG 1780

Qy       1741 GGCGGGTGCCGGAGGGCGAGGAGGCCTGCGGGGAGGCCCATACACCCCCAGCCGTCCACT 1800
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1781 GGCGGGTGCCGGAGGGCGAGGAGGCCTGCGGGGAGGCCCATACACCCCCAGCCGTCCACT 1840

Qy       1801 CCAACCACGCCCCAGTCACCCAGGCCCGCGAGGGCAACCTGCCGCTCCTCATTGCGCCCG 1860
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1841 CCAACCACGCCCCAGTCACCCAGGCCCGCGAGGGCAACCTGCCGCTCCTCATTGCGCCCG 1900

Qy       1861 CCCTGGCCGCGGTGCTCCTGGCCGCGCTGGCTGCGGTGGGGGCAGCCTACTGTGTGCGGC 1920
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1901 CCCTGGCCGCGGTGCTCCTGGCCGCGCTGGCTGCGGTGGGGGCAGCCTACTGTGTGCGGC 1960

Qy       1921 GGGGGCGGGCCATGGCAGCAGCGGCTCAGGACAAAGGGCAGGTGGGGCCAGGGGCTGGGC 1980
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1961 GGGGGCGGGCCATGGCAGCAGCGGCTCAGGACAAAGGGCAGGTGGGGCCAGGGGCTGGGC 2020

Qy       1981 CCCTGGAACTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCGAAGGCAACAGAGGGCG 2040
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2021 CCCTGGAACTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCGAAGGCAACAGAGGGCG 2080

Qy       2041 GTGGAGAGGCCCTGCCCAGCGGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCCAGGGC 2100
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2081 GTGGAGAGGCCCTGCCCAGCGGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCCAGGGC 2140

Qy       2101 CTGGCCTCCAGTCACCCCTCCACGCAAAGCCCTACATCTAAGCCAGAGAGAGACAGGGCA 2160
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2141 CTGGCCTCCAGTCACCCCTCCACGCAAAGCCCTACATCTAAGCCAGAGAGAGACAGGGCA 2200

Qy       2161 GCTGGGGCCGGGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTGCTGCCACACCACGTA 2220
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                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2201 GCTGGGGCCGGGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTGCTGCCACACCACGTA 2260

Qy         2221 AGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGACCACAGCTGGGCC 2280
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2261 AGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGACCACAGCTGGGCC 2320

Qy         2281 CTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCC 2340
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2321 CTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCC 2380

Qy         2341 CTAACGTCCCCAGAACCGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTG 2400
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2381 CTAACGTCCCCAGAACCGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTG 2440

Qy         2401 CAGTCCCTGGGCACGGCGGGCCCTGCCATGTGCTGGTAACGCATGCCTGGGTCCTGCTGG 2460
                ||||||||||||||||||||||||||||||||||||||||||||||||||| ||||||||
Db         2441 CAGTCCCTGGGCACGGCGGGCCCTGCCATGTGCTGGTAACGCATGCCTGGGCCCTGCTGG 2500

Qy         2461 GCTCTCCCACTCCAGGCGGACCCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAG 2520
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2501 GCTCTCCCACTCCAGGCGGACCCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAG 2560

Qy         2521 GGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAA 2580
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2561 GGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAA 2620

Qy         2581 GAAACTGGAAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAAA--ATATATATATT 2638
                |||||||||||||||||||||||||||||||||||||||||||||||  |||||||||||
Db         2621 GAAACTGGAAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAAAATATATATATATT 2680

Qy         2639 TATAAGAGATCCTTTCCCATTTATTCTGGGAAGATGTTTTTCAAACTCAGAGACAAGGAC 2698
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2681 TATAAGAGATCCTTTCCCATTTATTCTGGGAAGATGTTTTTCAAACTCAGAGACAAGGAC 2740

Qy         2699 TTTGGTTTTTGTAAGACAAACGATGATATGAAGGCCTTTTGTAAGAAAAAATAAAAGATG 2758
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         2741 TTTGGTTTTTGTAAGACAAACGATGATATGAAGGCCTTTTGTAAGAAAAAATAAAAGATG 2800

Qy         2759 AAGTGTGAAA 2768
                ||||||||||
Db         2801 AAGTGTGAAA 2810
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